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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/981,583	02/03/98	DICKMANNS A	028622/0/0

HM22/0315

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EXAMINER	
HARRIS, A	
ART UNIT	**PAPER NUMBER**
1642	22

DATE MAILED: 03/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/981,583	Applicant(s) Dickmanns t al.
	Examiner Alana M. Harris, Ph. D.	Group Art Unit 1642

☒ Responsive to communication(s) filed on *Nov 28, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-12, 16-22, 29-31, 33-35, and 38* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12, 16-22, 29-31, 33-35, and 38* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Amendment

1. The Examiner notified Applicants on December 13, 2000 that the finality of recorded presented in Paper Number 18, mailed August 28, 2000 was withdrawn for the reasons set forth below in this detailed action.

2. Claims 1-12, 16-22, 29-31, 33-35 and 38 are pending.

Claim 35 has been amended.

Claims 1-12, 16-22, 29-31, 33-35 and 38 are examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections

Claim Rejections - 35 U.S.C. § 112

4. The rejection of claim 35 is under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention is withdrawn in view of Applicants' amendment to the claim.

Claim Rejections - 35 U.S.C. § 102

5. The rejection of claims 1-3, 6-10, 16-19, 21, 22 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Garcia et al. (Molecular and Cellular Biology 6(6):1974-1982) is withdrawn in view of Applicants' arguments.

Claim Rejections - 35 U.S.C. § 103

6. The rejection of claims 1, 4, 5 and 16-20 under 35 U.S.C. 103(a) as being unpatentable over Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982), in view of Schlimok et al. and Yanagihara et al. is withdrawn in view of Applicants' arguments.

7. The rejection of claims 1, 11, 12, 16, 29 and 30 under 35 U.S.C. 103(a) as being unpatentable over Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982), in view of Blankenstein et al. (Current Biology 3:694-698, 1991) is withdrawn.

8. The rejection of claims 1, 16-19, 21 and 31 under 35 U.S.C. 103(a) as being unpatentable over Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982), in view of Sigma Cell Culture Catalogue and Price List (1995) is withdrawn.

9. The rejection of claims 1, 33 and 34 under 35 U.S.C. 103(a) as being unpatentable over Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982), in view of Gottlinger et al. (Int. J. Cancer 38:47-53, 1986) is withdrawn.

New Grounds of Rejection

Claim Rejections - 35 U.S.C. § 103

10. Claims 1-10, 16-22 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carney et al. (Cancer Research 45:2913-2923, June 1985), in view of Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982). Carney teaches disseminated small cell lung cancer human tumor cell lines (see page 2914, Materials and Methods). These autologous cells with metastatic potential are derived from bone marrow and pleural exudate. Carney does not teach the said cell has integrated in its genome or another replicative genetic element the DNA encoding the early region (large T antigen) of non-infectious SV40 DNA in its genome nor at least one additional oncogene. Additionally, Carney does not teach at least one defect in the origin of replication or the *in vitro* process by which the tumor cell incorporates the DNA encoding at least one immortalizing oncogene into a non-immortalized epithelial tumor cell. Carney lacks the method step of incorporating DNA via microinjection, which is performed after the step of carrying out a primary expansion of said epithelial tumor cells comprising the step of culturing in a medium with epidermal growth factor on the extracellular matrix, collagen coated tissue flasks.

However, Garcia does teach an autologous, disseminated immortalized rabbit mammary epithelial tumor cell which has integrated in its genome or another replicative genetic element the DNA encoding the early region (large T antigen) of non-infectious SV40 DNA. The epithelial tumor cell contains at least one defect in the origin of replication. Garcia also teaches an epithelial tumor cell that has integrated in its genome at least one additional oncogene, wherein the additional oncogene is c-Ha-ras. Garcia continues to teach the *in vitro* process by which the tumor cell incorporated the DNA encoding at least one immortalizing oncogene. The step of incorporating DNA comprising microinjection, which was performed after the step of carrying out a primary expansion of said epithelial tumor cells. The primary expansion comprised the step of culturing in a medium comprising epidermal growth factor on the extracellular matrix, collagen coated tissue flasks.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the cell line of Carney (available through the ATCC) to establish a metastatic cell line suitable for studying the immortalizing and transforming potential of known and candidate genes for epithelial cells. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Carney and Garcia that the establishment of such a cell line could be readily made and successfully propagated in order to conduct experiments geared to the long term study of metastasis in many assay systems.

11. Claims 1-12, 16-22, 29, 30 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carney et al. (Cancer Research 45:2913-2923, June 1985) in view of Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982) and Blankenstein et al. (Current Biology 3:694-698, 1991). The teachings of Carney of an epithelial tumor cell with metastatic potential and Garcia of methodology to immortalize, incorporate DNA and culturing said cell have been discussed in the paragraphs above. These references do not teach the epithelial tumor cell having integrated in its genome or another replicative genetic element an externally introduced gene encoding a cytokine immunostimulatory factor, such as interleukin-4 (IL-4).

However, Blankenstein et al. teach the transfer of single cytokine genes into cancer cells. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention was made to introduce genes encoding cytokine immunostimulatory factors, such as IL-4, granulocyte colony-stimulating factor and tumor necrosis factor into the tumor cell of Carney. One of ordinary sill in the art would have been motivated to do so with a reasonable expectation of success by the teachings well known in the art, that the transfer and the expression of such immunostimulatory factor genes into cancer cells would mediate powerful tumor suppression potential in T-cell deficient animals and appear to be effective even for poorly or non-antigenic tumors. Additionally, Blankenstein et al. report that "cancer cells transfected to produce certain cytokines might induce effective tumor-specific immunity in cancer patients".

12. Claims 1-10, 16-22, 31 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carney et al. (Cancer Research 45:2913-2923, June 1985), in view of Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982) and Sigma Cell Culture Catalogue and Price List (1995).The teachings of Carney and Garcia of production of a cultured immortalized metastatic epithelial tumor cell in a medium comprising epidermal growth factor (EGF) have been discussed in the paragraphs above. These reference do not teach a medium comprising recombinant human epidermal growth factor (rhEGF) or the basic fibroblast growth factor (bFGF), recombinant human basic fibroblast growth factor (rhbFGF).

However, the Sigma Cell Culture Catalogue teaches the availability of these growth factor supplements at the time the claimed invention was made. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use rhEGF and rhbFGF to supplement the culture medium. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Carney, Garcia and the Sigma Cell Culture Catalogue to order these supplements and use them in view of the recommended concentrations and practices listed in the technical section of the catalogue.

13. Claims 1-10, 16-22, 33, 34 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carney et al. (Cancer Research 45:2913-2923, June 1985), in view Garcia et al.(Molecular and Cellular Biology 6(6):1974-1982) and Gottlinger et al. (Int. J. Cancer 38:47-53, 1986). The teachings of Carney and Garcia of an immortalized epithelial tumor cell with

metastatic potential have been discussed in the paragraphs above. These reference do not teach a composition comprising the said epithelial tumor cell, nor the said composition comprising a vaccine in combination with a vaccine adjuvant.

However, Gottlinger et al. teach compositions containing epithelial cell surface antigens and *Bordetella pertussis* adjuvant suitable for mounting an immunological response. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to manufacture a composition comprising the epithelial tumor cell of claim 1 in combination with a *B. pertussis* adjuvant. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings of all three references that the production of an adjuvant prepared by culturing autologous epithelial tumor cells coupled with *B. pertussis* adjuvant would be suitable for administration to a non-human animal for augmenting immune responses in order to generate antibodies that would allow one skilled in the art to biochemically characterize a specific antigen defined by the generated antibodies.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on Monday through Friday from 6:30 am to 3:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached on (703)308-3995. Any inquiry of a general nature or relating to the status of this application or

proceeding should be directed to the Group receptionist whose telephone number is (703)308-0196.

Alana M. Harris, Ph.D.
Patent Examiner, Group 1642
March 14, 2001